Rapidly Increasing Incidence of Ocular Non-Hodgkin Lymphoma

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A recent report suggesting that ocular adnexal non-Hodgkin lymphoma (NHL) may be related to *Chlamydia psittaci* infection underscores the need for reliable epidemiologic data for this malignancy. We examined population-based incidence data from the Surveillance, Epidemiology, and End Results (SEER) Program. During 1992–2001 in the 12 SEER areas, ocular (i.e., eye and adnexa) NHL rates per 100 000 person-years for both sexes were highest among Asians/Pacific Islanders, lower in whites, and lower still in blacks. Incidence increased with advancing age and showed little difference by sex, in contrast to other (extranodal and nodal) NHLs, which occurred predominantly in males. From 1975–2001, there was a rapid and steady increase in incidence of ocular NHL, with annual increases of 6.2% and 6.5% among white males and females, respectively, with no evidence of peaking. By contrast, other NHLs showed evidence of peaking in recent years. The distinctive patterns of ocular NHL call for further studies to identify risk factors and mechanisms, including the potential role of *C. psittaci* or other infections. [J Natl Cancer Inst 2006;98:936–9]

The high prevalence of *Chlamydia psittaci* infection reported in patients with ocular adnexal non-Hodgkin lymphoma (NHL), and the complete remission or significant reduction of measurable lesions following antibiotic therapy, suggested a role for *C. psittaci* infection in the etiology of this rare cancer *(1,2)*. These findings underscore the need for improved understanding of the epidemiology of this disease, including temporal trends in its incidence. The most common histologic type of primary ocular adnexal NHL is reported to be marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT) type *(3)*. Descriptive data on ocular NHL are sparse, but a recent survey utilizing the Florida Cancer Data System Registry reported an increase in the incidence of orbital lymphomas between 1981 and 1993 *(4)*.

Table 1. Incidence of ocular, other extranodal, and nodal non-Hodgkin lymphoma (NHL) by sex in 12 areas of the National Cancer Institute Surveillance, Epidemiology and End Results program,* 1992–2001

Type of NHL	Male count	Male rate†	Female count	Female rate†	Male/female Rate ratio	Ethnicity rate Ratio, males	Ethnicity rate Ratio, females
Ocular NHL							
White	323	0.27	408	0.27	1.00	1.00‡	1.00‡
Black	23	0.18	32	0.19	0.95	0.67	0.70
American Indian/Alaska native	0	0.00	2	0.11	0.00	0.00	0.41
Asian/Pacific Islander	47	0.33	58	0.32	1.03	1.22	1.19
Nonocular extranodal NHL							
White	9746	7.86	7227	4.75	1.65	1.00‡	1.00‡
Black	959	6.47	626	3.62	1.79	0.82	0.76
American Indian/Alaska native	59	4.14	41	2.48	1.67	0.53	0.52
Asian/Pacific Islander	955	6.66	774	4.51	1.48	0.85	0.95
Nodal NHL							
White	20 377	16.72	16 965	11.16	1.50	1.00‡	1.00‡
Black	1677	12.19	1194	7.03	1.73	0.73	0.63
American Indian/Alaska native	77	5.30	72	4.31	1.23	0.32	0.39
Asian/Pacific Islander	1375	9.68	1091	6.29	1.54	0.58	0.56

*San Francisco–Oakland, Connecticut, Metropolitan Detroit, Hawaii, Iowa, New Mexico, Seattle–Puget Sound, Utah, Metropolitan Atlanta, San Jose–Monterey, Los Angeles, and Alaska.

†Age-adjusted using 2000 U.S. standard per 100 000 person-years.

‡Referent group.

In this study, we used population-based incidence data from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program *(5)* to calculate incidence rates of primary ocular NHL (in this report, ocular NHL refers to tumors arising in either the eye or its adjunct parts, the adnexa) and compared them to incidence rates of other extranodal and nodal NHL *(6)*. Based on data from 12 SEER areas (see Table 1) in the United States spanning 1992–2001, we computed rates by sex, race/ethnicity, age group, and geographic area. In addition, we used yearly data for 1975–2001 from nine SEER areas to estimate annual percentage changes (APC) in incidence and the 95% confidence intervals (CIs) using SEER*Stat *(7)*. The temporal trends were plotted such that a slope of 10 degrees represented a change of 1% per year *(8)*. All rates were calculated per 100 000 person-years and were age-adjusted using the 2000 U.S. standard.

During 1992–2001 in the 12 SEER areas, 42 828 cases of nodal NHL (site recode = 33 041) and 21 280 cases of extranodal NHL (site recode = 33 042), including 893 cases of primary ocular [International Classification of Diseases for Oncology, Third Edition, topography codes = 690–699 *(9)*] were diagnosed (667 NHL cases in individuals of unknown race were excluded). Most ocular lymphomas arose from the adnexa (831 cases), including the conjunctiva (code = 690; 264 cases), lacrimal gland (code = 695; 106 cases), and orbit (code =

696; 457 cases), or from overlapping lesion of the eye and adnexa (code = 698; four cases). Less common were tumors of the eye (27 cases), including the cornea (code = 691; one case), retina (code = 692; four cases), choroid (code = 693; five cases), ciliary body (code = 694; 17 cases), and ocular tumors not otherwise specified (code = 699; 35 cases). As shown in Table 1, ocular NHL rates were the same for males and females. By contrast, other extranodal and nodal NHLs were more common in males than females. Ocular NHL rates for both sexes were highest among Asians/Pacific Islanders, followed by whites, with the lowest rates for blacks and (based on small numbers) American Indians/Alaska natives. This pattern is consistent with previous reports of the high relative frequency of ocular lymphoproliferative tumors in Asian countries as compared with western populations *(10–12)*. For nonocular extranodal NHL, both male and female rates were highest among whites, followed by Asians/Pacific Islanders and blacks, whereas for nodal NHL the rates were highest among whites, followed by blacks. In all ethnic groups, the rates of ocular and other NHL increased steadily with advancing age (data not shown).

When analyzed by geographic area, the incidence rates for ocular NHL ranged from 0.18 in Utah to 0.31 in the Detroit area. For other forms of NHL (extranodal and nodal), the rates among whites were lowest in New Mexico and highest in

the San Francisco-Oakland area, where human immunodeficiency virus–related lymphomas are most common, especially in middle-aged men *(13–15)*.

Among whites in the nine SEER areas, ocular NHL incidence rates increased rapidly and steadily from 1975 to 2001, at 6.2% (95% CI = 4.4% to 7.9%) and 6.5% (95% CI = 5.1% to 7.9%) per year among males and females, respectively, with no evidence of peaking (Fig. 1). During the same time period, the rates for other extranodal NHLs increased at 4.3% (95% CI = 3.2% to 5.4%) and 4.0% (95% CI = 3.5% to 4.5%) per year among males and females, respectively, while the rates for nodal NHL rose less rapidly, at 1.8% (95% CI = 1.3% to 2.2%) and 1.3% (95% CI = 1.0% to 1.6%). Extranodal nonocular NHL rates among males and nodal NHL rates among both sexes peaked in the mid-1990s, with the leveling off due in part to the recent decline in human immunodeficiency virus-related lymphomas *(13–17)*.

It is difficult to determine whether the upward trend in ocular NHL is real or results, as suggested by others, from diagnostic improvements *(3,18)* or changes in classification schemes, particularly because many adnexal NHLs were previously classified as benign lesions such as reactive hyperplasia or pseudolymphoma *(19)*. The distinction between benign and malignant tumors became clearer with the recognition of MALT lymphomas in 1983 associated
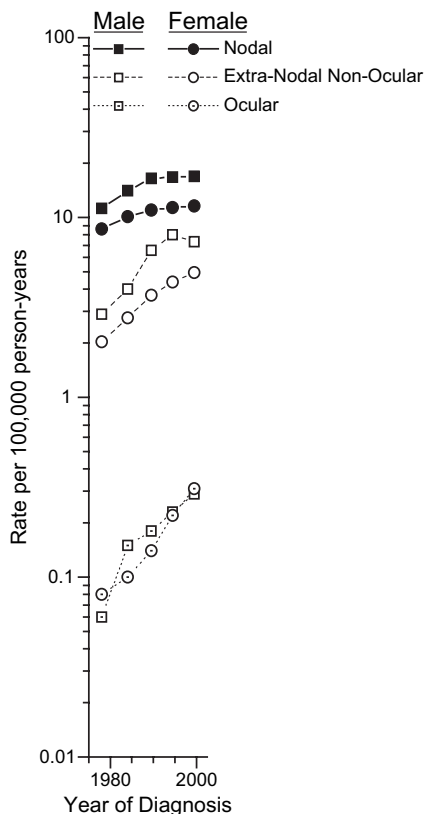
Fig. 1. Age-adjusted (2000, U.S.) non-Hodgkin lymphoma incidence trends among whites by site and sex for the years 1975–2001. Data points indicate rates calculated for 1975–1980, 1981–1986, 1987–1991, 1992–1996, and 1997–2001 using data from nine areas of the National Cancer Institute Surveillance, Epidemiology and End Results program: San Francisco–Oakland, Connecticut, Metropolitan Detroit, Hawaii, Iowa, New Mexico, Seattle–Puget Sound, Utah, and Metropolitan Atlanta.

with the advent of immunohistochemical and molecular techniques *(20)*. However, ocular pseudolymphomas are not reported in SEER, nor are the SEER data sufficient to distinguish low-grade ocular NHL (a category that includes most MALT lymphomas) from high-grade ocular NHL. It is noteworthy that the diagnostic code for MALT tumors was used sparsely before 1995 and did not become official until 2001 *(9)*. In the SEER data, the percentage of ocular NHL cases that were coded as MALT lymphoma among different ethnic groups increased from 7–11% during 1993–1996 to 40–60% during 1997–2001. Ninety-eight percent of the ocular NHLs classified as MALT lymphoma occurred in adnexal sites.

To evaluate the effect of changes in disease classification on the increasing incidence of ocular NHL, we compared incidence trends for ocular NHL with those for NHL at three other extranodal sites of MALT lymphoma (stomach, salivary gland, and lung) during two time periods: 1975–1990 when MALT lymphomas were not recorded in SEER and 1991–2001 when the MALT code was used. We reasoned that if the increasing incidence recorded for ocular NHL was due to the recent recognition of MALT lymphomas, then a similar increase would be observed at these other sites, where the overall percentages of lymphomas recorded as MALT from 1991 to 2001 have been similar (19.3% in the salivary gland, 18.4% in the stomach, and 12.6% in the lung compared to 20.4% in the eye/adnexa). The APC for ocular NHL for both sexes combined were 8.2% (95% CI = 4.3% to 12.2%) and 6.0% (95% CI = 3.8% to 8.3%) for 1975–1990 and 1991–2001, respectively. By comparison, the corresponding APC were 4.6% (95% CI = 3.1% to 6.1%) and –0.1% (95% CI = –0.9% to 0.7%) for gastric NHL, 6.0% (95% CI = 3.1% to 8.9%) and 3.8% (95% CI = 0.6% to 7.1%) for salivary gland NHL, and 8.9% (95% CI = 5.3% to 12.7%) and –4.0% (95% CI = –6.3% to –1.6%) for lung NHL. Because the incidence of ocular NHL rose more rapidly than did NHL at other MALT-related sites in both time periods (except for lung NHL during 1975–1990), while the percentages that were MALTs were similar across sites, it seems likely that the shift from lymphoid hyperplasia to low-grade MALT lymphomas accounts only partly for the upward trend in ocular NHL that we observed. Therefore, at least some of the increased incidence appears to be real.

Could *C. psittaci* infection, which has been linked recently to ocular adnexal lymphoma *(1,2)*, account for the unusual patterns of incidence? Infection by this pathogen in humans, which is caused mainly by exposure to infected birds and household pets, may produce psittacosis, a febrile illness that is often manifested by pneumonia *(21)*. In the United States, the annual incidence of psittacosis, a reportable disease, has shown little change over time *(22)*. However, considerable underdiagnosis and underreporting are likely, particularly for mild or atypical cases such as those with chronic follicular conjunctivitis due to *C. psittaci* transmitted directly from infected birds or cats *(23,24)*. Our findings and a recent report suggesting no association between *C. psittaci* and cases of ocular adnexal lymphoma diagnosed in South Florida *(25)* call for further studies to determine whether ocular *C. psittaci* or other infections may provoke a chronic lympho-proliferative response resembling the gastric MALT lymphomas associated with *Helicobacter pylori* infection *(26–29)*, and to identify other factors that contribute to the distinctive patterns of this rare but rapidly rising malignancy.

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